Fetal Heart Defects and Measures of Cerebral Size

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Objectives To estimate the association between fetal congenital heart defects (CHDs) and measures of brain size throughout pregnancy, from the end of the first trimester to birth.

Study design The cohort consisted of all fetuses scanned in Western Denmark in 2012 and 2013. Anthropometric measures in fetuses with isolated CHDs diagnosed within 12 months after birth were compared with those in the fetuses without CHDs. Z-scores standardized to gestational age were calculated for first trimester biparietal diameter, second trimester head circumference, fetal weight, birthweight, head circumference, and placental weight.

Results We obtained data from 63 349 pregnancies and identified 295 fetuses with isolated CHDs (major n = 145; minor n = 150). The first trimester mean biparietal diameter Z-scores were not different between those with and those without CHDs. The head circumference mean Z-score difference was −0.13 (95% CI, −0.24 to −0.01; $P = .03$) in the second trimester and −0.22 (95% CI, −0.35 to −0.09; $P < .001$) at birth. Fetuses with univentricular physiology or tetralogy of Fallot showed the most pronounced compromise in cerebral size.

Conclusions Our results suggest that the brain alterations inducing an increased risk of impaired neurodevelopment in children with CHDs begin during pregnancy. Although fetuses with univentricular physiology or tetralogy of Fallot exhibited the most pronounced compromise in cerebral size, we recommend neurodevelopmental follow-up for all children with CHDs. *(J Pediatr 2019;210:146-53)*.

Congenital heart defects (CHDs) affect 6-8 children per 1000 live births,[1] and the risk of impaired neurodevelopment among these children is well-established.[2-11] The association between CHDs and small head size at birth is well-described,[1,12,13] and impaired neurodevelopment has been associated with small head size at birth.[14] Magnetic resonance imaging of the fetal brain has been used to explore the potential explanations for these associations and has shown that fetuses with major CHDs exhibit smaller cerebral volumes and delayed cerebral maturation,[6,15-17] as well as a decrease in cerebral oxygen supply and tissue oxygenation during late gestation.[18,19] Recent studies have reported an increased risk of placental pathology and possibly preeclampsia,[20-22] as well as a reduced placental size at birth[23] in women carrying a fetus with a CHD. Studies have reported indices of impaired brain growth as early as mid-gestation in fetuses with prenatally detected CHDs.[24,25]

Most fetuses with isolated CHDs survive birth and heart surgery[26,27]; thus, the search for potential neuroprotective strategies is increasingly relevant and has recently been expanded into fetal life.[28] It is unknown at which time point during the course of pregnancy the fetal heart defects may affect brain growth; thus, we aimed to estimate the association between fetal CHDs and measures of fetal size and brain size throughout pregnancy, from the end of the first trimester to birth.

Methods

In this population-based cohort study, we included data on the fetuses and newborn children in Western Denmark (a total population of 3 million) of pregnant women who attended at least 1 of the 2 pregnancy ultrasound scans between January 1, 2012, and December 31, 2013. We identified fetuses with CHDs defined as structural defects in the heart or intrathoracic great vessels of actual or potential functional significance (modified from[29]) diagnosed during pregnancy or up to 12 months after birth to include as many children with CHDs as possible.

All pregnant women in Denmark are offered 2 routine ultrasound scans free of charge during pregnancy, a first trimester scan at a gestational age of $11^{3/7}$ to $13^{6/7}$ weeks that includes a risk assessment for chromosomal anomalies and a fetal anomaly scan at a gestational age of $18^{0/7}$ to $21^{6/7}$ weeks. These scans

CHD	Congenital heart defect
HC	Head circumference
RAA	Right aortic arch
VSD	ventricular septal defect

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The authors declare no conflicts of interest.

Portions of this study were presented at the jENS (joint European Neonatal Societies) conference, October 31-November 4, 2017, Vienna, Italy.

https://doi.org/10.1016/j.jpeds.2019.02.042

are attended by more than 90% of all pregnant women,[30,31] and the data are stored in a local fetal medicine database (2004-2018 Astraia Software GmbH, Munich, Germany) used by all obstetric departments in Denmark. All data are transferred to a nationwide database, the Danish Fetal Medicine Database.[30] Women carrying fetuses with malformations, increased nuchal translucency, or increased risk of trisomy after the combined first trimester screening are offered invasive testing and high-resolution chromosomal microarray or standard chromosome analysis. Fetuses and children with suspected CHDs are referred to a tertiary center at Aarhus University Hospital for further examination and counseling of their parents.

Prenatal ultrasound biometrics, birthweight, and placental weight were obtained from the Danish Fetal Medicine Database. Head circumference (HC) and length at birth were obtained from The Danish Medical Birth Registry.[32] Using the personal identification number assigned to all live-born children and all citizens residing in Denmark (allowing unambiguous individual-level record linkage of all Danish registers[33]), we identified fetuses with CHDs by the integration of four sources of data: the local Fetal Medicine Database, the local register of prenatal genetic test results, cardiac diagnoses from the Patient Administration System Central Region Denmark, and the Danish Fetal Medicine Database. According to our definition of CHDs, arrhythmias, cardiomyopathies, tumors, and minor anatomic abnormalities, such as patent ductus arteriosus before 37 weeks of gestation, persistent oval foramen, and pulmonary branch stenosis, were not included. Individuals with diagnoses that could not be verified by the pathological records, second opinion fetal ultrasound scan records, or postnatal ultrasound scan records (n = 4) were also excluded from the CHD cohort.

The initial cohort consisted of 63 349 pregnancies including 412 fetuses (0.66%) with CHDs. **Figure 1** presents the delimitation of the final cohort.[29,34]

If a woman was pregnant more than once during the 2-year period, only data from the first of the pregnancies were included. Owing to delays in registration, pregnancy outcomes were not available for some of the fetuses scanned during the last 6 months of the study period.

Birth biometric data from children born before 30 weeks of gestation were excluded owing to the lack of plausible reference values of birthweight and HC at this age as well as the higher risk of associated maternal or fetal illness in these children born very preterm.[35] Observations deviating more than 5 SD from the mean were excluded from the analyses in both groups.[1,36]

CHDs were initially stratified into major and minor CHDs (**Table I**) and further stratified into 6 subgroups: (1) univentricular (heart with any univentricular physiology including hypoplastic left heart syndrome), (2) Tetralogy of Fallot, (3) transposition of the great arteries, (4) aortic obstructions (severe aortic stenosis, aortic atresia, hypoplastic aortic arch, and/or coarctation of the aortic arch[38]), (5) ventricular septal defect (VSD), and (6) atrial septal defect (**Table II** and **Figure 2**). The remaining fetuses were not considered in the subgroup analyses owing to sparse data.

We compared measures of fetal anthropometry at 3 different time points during pregnancy (end of the first trimester, middle of the second trimester, and at birth). According to the national guidelines, the biparietal diameter at the first trimester scan (between a gestational age of $11^{3/7}$ and $13^{6/7}$ weeks) was the preferred measure of brain size. At the anomaly scan (gestational age of $18^{0/7}$ to $21^{6/7}$ weeks), the HC was calculated based on the biparietal diameter and the occipital frontal diameter.[39] The estimated fetal weight was calculated according to the Hadlock formula.[40]

At birth, HC, weight, and length of the newborn and the weight of the placenta are routinely measured within the first hour of life.[41] Data from all fetuses (live born, stillborn, and aborted) were included in the analysis. Data were analyzed using Stata 13.1 (StataCorp, College Station, Texas).

The fetal and neonatal biometric data were converted into Z-scores using published normative data from large populations of healthy fetuses and children[1,23,36,40] to account for differences in gestational age at both the fetal scanning and at birth.

The Student *t* test was used to calculate mean differences between groups. Mean differences are presented with 95% CIs and 2-sided *P* values at a 5% level of significance. The Wilcoxon rank-sum test was used to compare variables between groups when the variables were not normally distributed. The χ^2 test and the Fisher exact test were used to compare dichotomous variables. The association between gestational age and brain size Z-scores was estimated using linear regression with robust standard errors to account for repeated measurements within the same fetus. For the graphic presentation, we included all available brain size Z-scores regardless of the gestational age at the time of the scan. Gestational age was modeled using restricted cubic splines with prespecified knots at 12, 20, and 38 weeks of gestation. The study was approved by the Danish Data Protection Agency (1-16-02-391-14) and Danish Health and Medicines authority (journal number 3-3013-516/1/).

Results

The final cohort consisted of 57 785 fetuses, including 295 fetuses with isolated CHDs (**Table I** and **Figure 1**); 145 of the included fetuses (49.1%) had isolated major CHDs (**Table I**), 77 of these (53%) were diagnosed before birth. Forty-nine fetuses with isolated major CHDs were genetically tested, 44 of whom had chromosomal microarray performed. The women opted for termination of pregnancy in 29 pregnancies with isolated major CHDs (**Table I**). The basic characteristics and differences between individuals with and without CHDs are depicted in **Table III**. Overall, the risk of preterm birth was 5% in children without CHDs and 18.5% in children with CHDs.

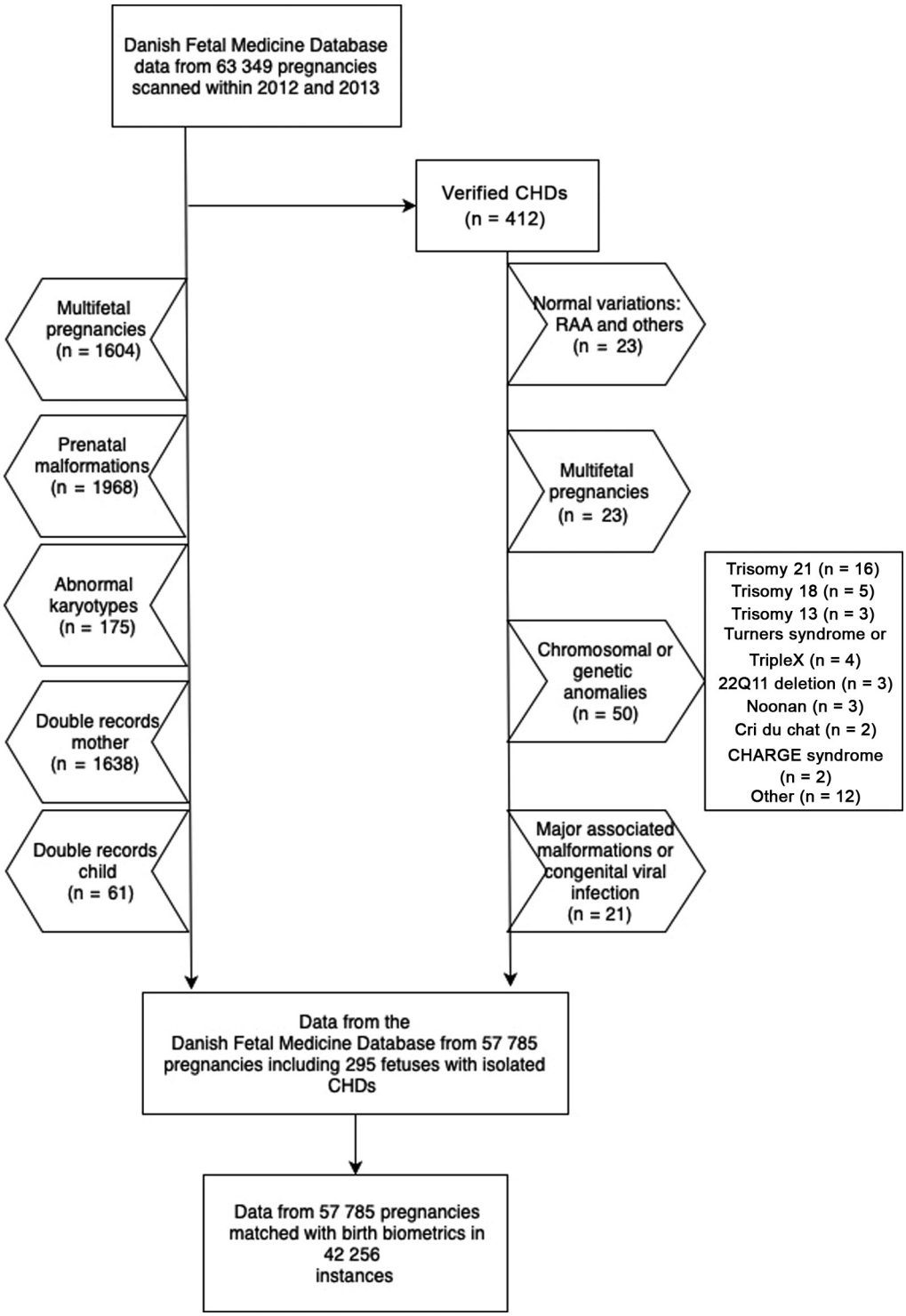

Figure 1. Delimitation of the ultrasound data and birth biometrics from the included fetuses with and without CHDs scanned between January 1, 2012, and December 31, 2013.

At the first trimester ultrasound scan (median gestational age of $12^{5/7}$ weeks), the mean Z-score difference between fetuses with and without CHDs was 0.03 (95% CI, −0.07 to 0.13; $P = .5$). At the anomaly scan (median gestational age of $20^{0/7}$ weeks), the mean HC Z-score difference was −0.13 (95% CI, −0.24 to −0.01; $P = .03$) between fetuses with and those without CHDs. At birth, the mean HC Z-score difference was −0.22 (95% CI, −0.35 to −0.09; $P < .001$). The differences between fetuses with major CHDs and those without CHDs were even more pronounced, with a mean

Table I. The distribution of major and minor CHDs

	All CHDs	Isolated CHDs	Isolated CHDs, terminated pregnancy	Isolated CHDs born after 23 weeks of gestation
Minor				
Atrial septal defect	58	41	0 (0)	41
VSD	83	70	0 (0)	70
Vascular ring	8	6	0 (0)	6
Mild pulmonary stenosis (no need for immediate intervention)	8	4	0 (0)	4
Mild hypoplasia or coarctation of the aortic arch	14	11	0 (0)	11
Patent arterial duct after 37 weeks of gestation	18	16	0 (0)	16
Other	3	2	0 (0)	2
Major				
Transposition of the great arteries	21	19	0 (0)	19
Hypoplastic left heart syndrome	26	19	13 (68)	6
Univentricular, other	26	21	14 (67)	6
Tetralogy of Fallot	26	17	0 (0)	17
Atrioventricular septal defect	17	6	0 (0)	6
Total or partial anomalous pulmonary venous connection	7	6	0 (0)	6
Double outlet right ventricle	9	7	1 (14)	6
Pulmonary atresia or severe pulmonary stenosis	17	11	0 (0)	10
Aortic atresia or severe aortic stenosis	7	6	0 (0)	6
Severe mitral or tricuspid insufficiency	4	2	0 (0)	2
Congenitally corrected transposition of the great arteries	3	3	0 (0)	3
Severe hypoplasia or coarctation of the aortic arch	29	24	1 (4)	23
Other	5	4	0 (0)	4

All CHDs, Total number of fetuses with the different types of CHDs; *Isolated CHDs*, number of CHD fetuses after the exclusion of multifetal gestations, genetic syndromes, and/or major associated malformations; *Isolated CHDs, terminated pregnancy*, number of isolated CHD pregnancies terminated (percentage); *CHDs born after 23 weeks of gestational age*, number of children with isolated CHD born after 23 weeks of gestational age.
Modified from.[37]

HC Z-score difference of −0.22 (95% CI, −0.38 to −0.06; $P < .009$) at the anomaly scan and −0.47 (95% CI, −0.67 to −0.28; $P < .001$) at birth. In the subgroup analyses, newborns with univentricular physiology or Tetralogy of Fallot had substantially smaller mean HC Z-scores at birth than newborns without CHDs (Table II).

Regression analyses of the absolute continuous Z-score of the head biometrics (biparietal diameter and HC; *y* axis) plotted against gestational age (*x* axis) illustrate that, especially fetuses with tetralogy of Fallot or univentricular physiology, present early with decreased mean brain size Z-scores compared with fetuses without CHDs. The differences were statistically significant from the middle of the second trimester and onward (Figure 2). The scatter points below each graph display the time points of available head size measurements for those with (CHD) and without (no CHD) a heart defect. If there were gaps between the measurements of some of the heart defects, the continuous curve is based on some degree of interpolation and the CI is wider.

The mean differences between fetuses with and those without CHDs regarding fetal weight and birthweight Z-scores were −0.17 (95% CI, −0.25 to −0.08; $P < .001$) and −0.22 (95% CI, −0.34 to −0.10; $P < .001$), respectively. The mean difference between birthweight Z-score among fetuses with major CHDs compared with infants without CHDs was −0.42 (95% CI, −0.59 to −0.24; $P < .001$). Of note, the estimated fetal weight Z-score and the birthweight Z-scores in fetuses and newborns with VSDs were significantly lower than those without CHDs (Table II).

Overall, the HC Z-scores compared with the birthweight Z-scores in newborns did not differ between those with and those without CHDs. However, in the subgroup analyses, newborns with univentricular physiology had a smaller HC in relation to birthweight. The mean Z-score difference in these newborns compared with infants without CHDs was −0.73 (95% CI, −1.31 to −0.15; $P = .01$). Newborns with aortic obstructions had larger HCs in relation to the birthweight. The mean Z-score difference was 0.37 (95% CI, 0.01 to 0.74; $P = .04$).

The mean placental weight Z-score difference between newborns with and without CHDs was −0.21 (95% CI, −0.33 to −0.09; $P < .001$). Further details about placenta weight Z-score differences are provided in Table II.

We found no statistically significant differences in HC Z-scores between individuals diagnosed with a CHD before birth compared to after birth, either at the anomaly scan or at birth.

Only 12 children were born with univentricular physiology after 23 weeks of gestation (Table I). We found no difference in HC Z-scores at the anomaly scan between those who were terminated and those who were not: −0.06 (95% CI, −1.03 to 0.91; $P = .9$).

Discussion

In the present study, brain size in fetuses with isolated CHDs was reduced at 20 weeks of gestation and onward, but not at 12 weeks of gestation. This finding was more prominent in fetuses with major CHDs, especially in those with univentricular physiology or Tetralogy of Fallot. In these subtypes, head

Table II. Mean Z-score differences of brain, body, and placental size between individuals with and without CHDs

Categories	BPD Z-score mean difference at the first trimester scan (median gestational age of $12^{5/7}$ weeks)	HC Z-score mean difference at the anomaly scan (median gestational age $20^{0/7}$ weeks)	Estimated fetal weight Z-score mean difference at the anomaly scan (median gestational age $20^{0/7}$ weeks)	HC Z-score mean difference at birth (median gestational age $40^{1/7}$ weeks)	Birth weight Z-score mean difference (median gestational age $40^{1/7}$ weeks)	HC minus birth weight Z-score mean difference (median gestational age $40^{1/7}$ weeks)	Placental weight Z-score mean difference (median gestational age $40^{1/7}$ weeks)
All CHDs	0.03 (−0.07 to 0.13)	−0.13 (−0.24 to −0.01)*	−0.17 (−0.25 to −0.08)*	−0.22 (−0.35 to −0.09)*	−0.22 (−0.34 to −0.10)*	0.04 (−0.08 to 0.16)	−0.21 (−0.33 to −0.09)*
Minor CHDs	0.11 (−0.03 to 0.25)	−0.04 (−0.20 to 0.12)	−0.07 (−0.19 to 0.05)	−0.03 (−0.20 to 0.14)	−0.05 (−0.21 to 0.11)	0.03 (−0.13 to 0.18)	−0.04 (−0.21 to 0.12)
Major CHDs	−0.05 (−0.19 to 0.09)	−0.22 (−0.38 to −0.06)*	−0.28 (−0.41 to −0.15)*	−0.47 (−0.67 to −0.28)*	−0.41 (−0.59 to −0.24)*	0.05 (−0.13 to 0.23)	−0.41 (−0.59 to −0.24)*
Univentricular	0.10 (−0.18 to 0.38)	−0.21 (−0.55 to 0.12)	−0.51 (−0.79 to −0.22)*	−0.85 (−1.48 to −0.21)*	−0.03 (−0.62 to 0.56)	−0.73 (−1.31 to −0.15)*	−0.03 (−0.62 to 0.57)
ToF	−0.12 (−0.51 to 0.27)	−0.27 (−0.73 to 0.18)	−0.13 (−0.47 to 0.22)	−0.94 (−1.245 to −0.43)*	−0.94 (−1.39 to −0.48)*	0.00 (−0.45 to 0.45)	−0.94 (−1.39 to −0.48)*
TGA	0.04 (−0.40 to 0.47)	−0.24 (−0.68 to 0.20)	0.07 (−0.28 to 0.41)	−0.15 (−0.66 to 0.35)	0.06 (−0.37 to 0.49)	−0.29 (−0.76 to 0.17)	0.06 (−0.37 to 0.49)
Aortic obstructions	−0.05 (−0.36 to 0.27)	−0.08 (−0.43 to 0.27)	−0.18 (−0.45 to 0.08)	−0.35 (−0.75 to 0.05)	−0.67 (−1.03 to −0.31)*	0.37 (0.01 to 0.74)*	−0.39 (−0.71 to −0.07)*
VSD	0.10 (−0.10 to 0.30)	−0.15 (−0.38 to 0.07)	−0.22 (−0.39 to −0.05)*	−0.17 (−0.42 to 0.07)	−0.37 (−0.60 to −0.13)*	0.20 (−0.02 to 0.42)	−0.35 (−0.59 to −0.12)*
ASD	0.04 (−0.22 to 0.30)	0.11 (−0.21 to 0.40)	0.10 (−0.12 to 0.32)	0.25 (−0.07 to 0.56)	0.35 (0.04 to 0.66)*	−0.06 (−0.35 to 0.23)	0.32 (0.04 to 0.66)*

Aortic obstructions, Aortic atresia/stenosis, aortic arch hypoplasia/coarctation; *ASD*, atrial septal defect; *BPD*, biparietal diameter; *ToF*, Tetralogy of Fallot; *TGA*, transposition of the great arteries.
*$P < .05$.

size was significantly smaller from the early second trimester and onwards.

Previous studies have also associated major CHDs with decreased cerebral size at mid gestation[24,38,42]; however, we also report on cerebral measures before 20 weeks of gestation in fetuses with major and minor CHDs.

We speculate whether the early onset of compromised cerebral growth in fetuses with univentricular physiology or Tetralogy of Fallot may be explained by intracardiac mixing of oxygenated and deoxygenated blood, leading to a state of relative cerebral hypoxia.[18,43] The early onset of deviations in fetal and placental growth may, on the other hand, point toward factors affecting both cardiogenesis and brain development,[44] such as genetic or epigenetic factors.

HC was smaller in newborns with isolated CHDs than in newborns without CHDs. Newborns with major CHDs accounted for the majority of this difference, confirming previous findings.[1,45] In newborns and fetuses with CHDs, we also found a smaller body size and that the placenta was smaller (potentially adding to the risk of a relative hypoxic state in utero[46]).

Aortic obstructions and VSDs were associated with increased HC relative to birthweight. This anthropometric pattern has previously been reported in newborns with a VSD.[1] During pregnancy, the flow across a VSD is minimal owing to pressure equilibration between the pulmonary and systemic circulations. Intrauterine growth restriction in fetuses without CHD, which has generally been associated with an asymmetrically large head relative to body size, has also been associated with lower left ventricular end-systolic and end-diastolic diameters, as well as a smaller posterior wall diameter in both systole and diastole.[47] Noteworthy is the decreased fetal weight already at the second trimester scan, and the low placental weight and weight at birth in children with VSDs in the present as well as in a previous study.[23] Even though a VSD is usually considered to be a minor CHD, we speculate that the presence of a VSD may alter the function of the heart during fetal life.

We do not know whether the brain suffers less if the body and the head are equally affected by reduced growth. Fetal brain-sparing physiology (reduced resistance to cerebral flow) has been associated with impaired neurodevelopment in children with CHDs,[48,49] and a low birthweight is reported to be a risk factor for impaired neurodevelopment.[50] Consequently, we are unable to determine whether neurodevelopment may be better in children with CHDs who are symmetrically small than in those where only the head is small.

We found a prevalence of CHDs of 6.6 per 1000 births (including live births, still births, and termination of pregnancies). Previous publications reported a birth prevalence between 5.4 and 15.3 per 1000 births.[1,37,51] The higher risk of preterm birth in individuals with CHDs observed in our study has previously been reported.[34] Children with a patent ductus arteriosus born before 37 weeks of gestation were excluded from our analyses; nonetheless, a patent ductus arteriosus screening program in children born very preterm

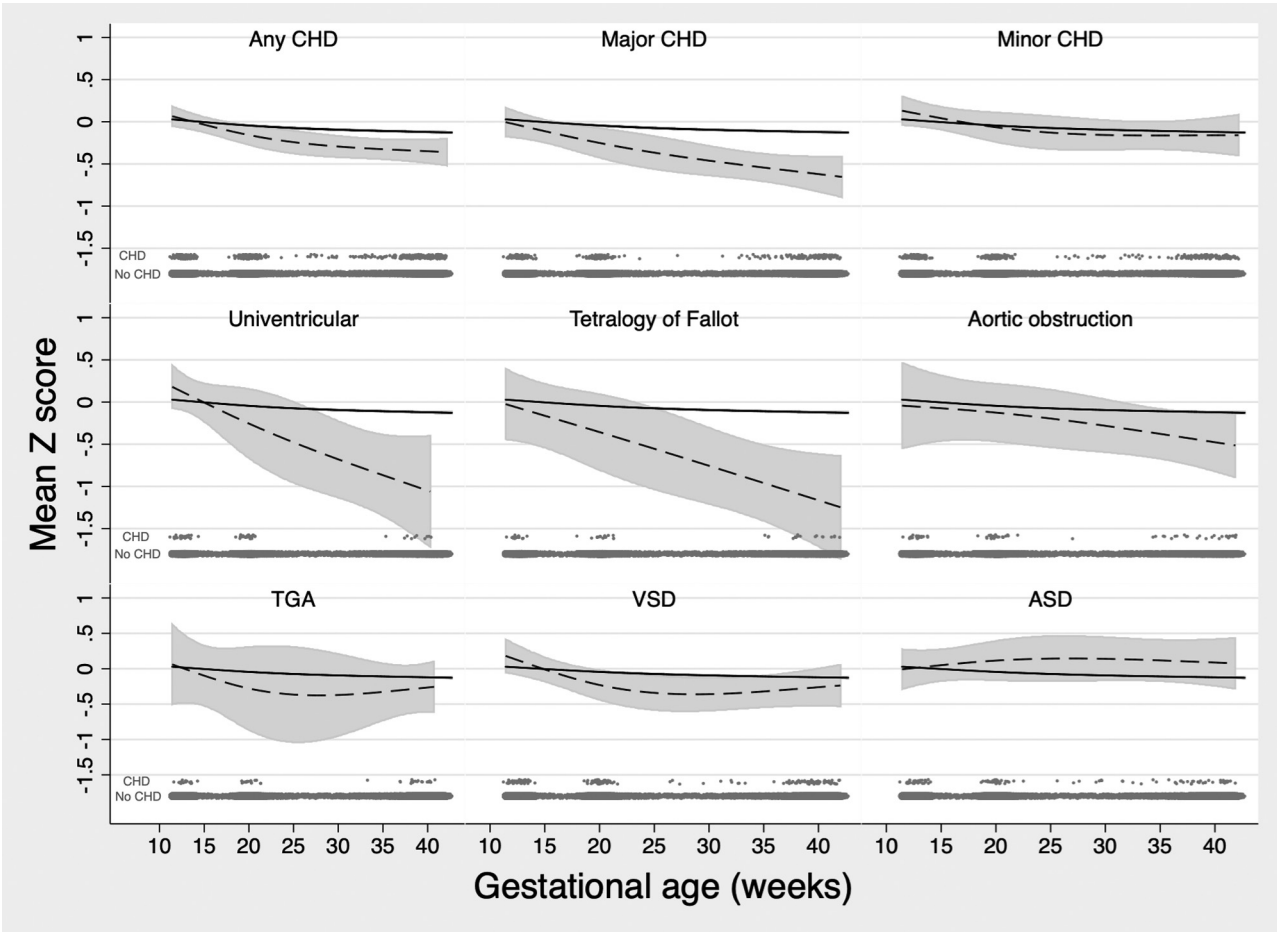

Figure 2. Mean continuous Z-scores of head biometrics (*y* axis) plotted against gestational age (*x* axis) in individuals without (*solid line*) and with (*dashed lines*) a CHD. *Grey area*, CIs. *Grey dots*, time points of available head size measurements for those with (CHD) and without (no CHD) a heart defect. *Aortic obstruction*, Aortic atresia/stenosis, aortic arch hypoplasia, or coarctation; *ASD*, atrial septal defect; *TGA*, transposition of the great arteries.

may have induced detection bias owing to the finding of small septal defects that otherwise would not have been found.[52]

A limitation of our study and prior studies in this field is that we cannot exclude confounding caused by genetic mutations and epigenetic alterations. Even though we excluded 50 fetuses owing to genetic or chromosomal anomalies, 95 (66%) of those with isolated major CHDs were not genetically tested. Because information was lacking, there may have been unknown factors (maternal characteristics, lifestyle, and obstetric and medical history) resulting in residual confounding.[53-56] The majority of the missing newborn

Table III. Basic characteristics and differences between individuals with and without CHDs

	No CHD	Isolated CHD	Difference
Gestational age at the first trimester scan, weeks	$12^{5/7}$ ($12^{2/7}$ to $13^{0/7}$)	$12^{4/7}$ ($12^{2/7}$ to $13^{0/7}$)	
Median BPD, mm	21.8 (20.1 to 23.3)	21.6 (20.0 to 23.3)	
Correction of gestational age at the first scan, days	+1 (−2 to 3)	0 (−3 to 2)	*
Gestational age at the anomaly scan, weeks	$20^{0/7}$ ($19^{5/7}$ to $20^{2/7}$)	$20^{0/7}$ ($19^{4/7}$ to $20^{3/7}$)	
Median HC at the anomaly scan, mm	171.4 (166.0 to 176.9)	170.7 (164.5 to 177.2)	
Gestational age at birth, weeks	$40^{1/7}$ ($39^{0/7}$ to $41^{0/7}$)	$39^{2/7}$ ($37^{5/7}$ to $40^{4/7}$)	*
HC at birth, cm	35 (34 to 36)	34 (33 to 36)	*
Birth weight, g	3530 (3190 to 3860)	3260 (2800 to 3655)	*
Placental weight, g	660 (570 to 760)	600 (500 to 720)	*

Values are median (IQR). Medians are compared using the Wilcoxon rank-sum test.
BPD, Biparietal diameter.
*$P < .05$.

biometric data originated from fetuses scanned during the last 6 months of the study period. These data are likely to be missing at random, and are thus unlikely to have introduced bias. In fetuses with univentricular physiology, the HC Z-scores at 20 weeks of gestation did not differ according to whether the child was later born alive. Consequently, we consider the risk of selection bias to be limited. HC Z-scores measured at birth in fetuses with CHDs were not statistically different in those diagnosed before and those diagnosed after birth. Nonetheless, some degree of measurement error and information bias cannot be ruled out. It is a major strength of the present study that we were able to include measurements as early as 12 weeks of gestation, linking later diagnoses during pregnancy as well as postnatal diagnoses of both major and minor CHDs with early prenatal measures.

Measures of brain size in fetuses with isolated CHDs begin to deviate from those of fetuses without CHDs during the second trimester. Fetuses with major CHDs and especially those with univentricular physiology or tetralogy of Fallot exhibited the earliest and most pronounced compromise in cerebral growth. We recommend neurodevelopmental follow-up of all children with CHDs. ■

We thank research nurse Vibeke Laursen for her assistance in obtaining the relevant data from the medical records. We thank Aarhus University for supporting this work.

Submitted for publication Nov 13, 2018; last revision received Jan 14, 2019; accepted Feb 27, 2019.

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